NUCLEATION AND CRYSTAL GROWTH OF ALPHA-GLYCINE

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ABSTRACT

Secondary nucleation is widely present in crystallisation processes and it is often relied upon to attain desirable critical quality attributes of crystalline products, such as polymorphic form and crystal size distribution. This is particularly the case in continuous crystallisation, where a good control of secondary nucleation can be crucial in order to achieve and maintain steady state operation.

This work utilises rapid, small-scale experiments in agitated vials with in-situ imaging for crystal counting and sizing (using the Crystalline platform), to quantify nucleation and crystal growth kinetics of α-glycine across a range of supersaturations in aqueous solutions under isothermal conditions. Both seeded and unseeded crystallisation experiments were conducted.

It was found that secondary nucleation and crystal growth rates determined from the same vials show a close correlation across the whole range of supersaturations investigated, which suggest a close relationship between the mechanisms of shear induced secondary nucleation and crystal growth in this system.

Keywords: Crystallisation, Nucleation, Crystal Growth

INTRODUCTION

Crystallisation from solution is a purification process used throughout the pharmaceutical and chemical industries to achieve desired crystalline particulate product properties, such as solid form, particle size, shape and purity. Control over these particulate properties facilitates downstream processing and resulting product performance. To achieve control of such a crystallisation process, an understanding of nucleation and growth, the two fundamental stages of crystal formation, is required.

In order to avoid problems associated with the intrinsic stochasticity of primary nucleation, secondary nucleation, the generation of new crystal nuclei from already-existing crystals, is often employed in industrial crystallisation. Secondary nucleation is often initiated at relatively low supersaturations to provide a controlled, steady supply of new crystals, accompanied by relatively slow crystal growth to achieve good purification and consistent process performance. This study aims to improve fundamental understanding of the relationships between crystal growth, nucleation and supersaturation in the metastable zone for crystallisation of α-glycine from aqueous solutions.

RESULTS AND DISCUSSION

Crystal growth rates for α-glycine estimated from in-situ imaging were in good agreement with values reported in literature from single crystal growth experiments. Plotting growth rates on a linear scale appears to indicate the presence of a ‘dead zone’ below a certain supersaturation, where growth does not seem to take place. However, if data is plotted on a log-log scale, they show a clear power law dependence on supersaturation, as may be expected from crystal growth theories. Therefore, there does not appear to be any dead zone for crystal growth of α-glycine.

Secondary nucleation rates [B] for both seeded and unseeded experiments were also estimated from in-situ imaging. The seed crystals were prepared and added to vials following a previously outlined workflow[1]. When the secondary nucleation rates were shown on a linear scale, data seem to indicate a secondary nucleation

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threshold around S=1.1. Again, when data is shown on a log-log scale, they are consistent with a power law dependence on supersaturation. Although it cannot be ruled out that secondary nucleation completely ceases at some lower supersaturations, it can become too slow to measure with a given experimental technique at some point, and it can also become insignificant in a practical industrial crystallisation context. Furthermore, secondary nucleation rates in seeded and unseeded experiments were very similar (Figure 1), which is consistent with the concept of the 'single nucleus mechanism'[2]: in other words even in unseeded conditions, crystallisation proceeds through the formation of a single crystal seed from solution by primary nucleation, with further nuclei then appearing through secondary nucleation from this original seed crystal.

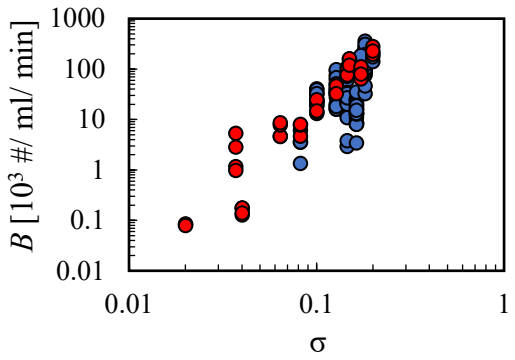

Figure 1. Comparison of secondary nucleation rates in seeded (red circles) and unseeded (blue circles) conditions plotted vs σ = S-1.

The primary nucleation rates were then estimated from induction time probability distributions[3] and plotted, along with secondary nucleation against the corresponding growth rates (Figure 2). The primary nucleation rate is much lower than secondary nucleation at all supersaturations suggesting that a high supersaturation is required to induce nucleation. Therefore, in a continuous crystallisation process, secondary nucleation is required to ensure that there is a constant supply of new crystals to achieve steady state operation.

Crystal growth and secondary nucleation are often studied and presented as two conceptually separate processes or mechanisms. Our approach allows us to compare the growth rate and the corresponding secondary nucleation rate from the same experimental vials, based on the same imaging-based measurement and image analysis. We see that there is a close relationship between growth and secondary nucleation kinetics across a wide range of supersaturations. This suggests a possible mechanistic relationship between the two phenomena, where the secondary nucleation induced by fluid shear is related to growth of the crystal boundary layer in contact with the supersaturated solution, where loosely bound crystalline domains are swept from the boundary layer and serve as crystal nuclei. This effect would be clearly distinct from mechanical breakage or attrition of seed crystals, as there is no reason why such a mechanical process would be related to the crystal growth rate and indeed solution supersaturation.

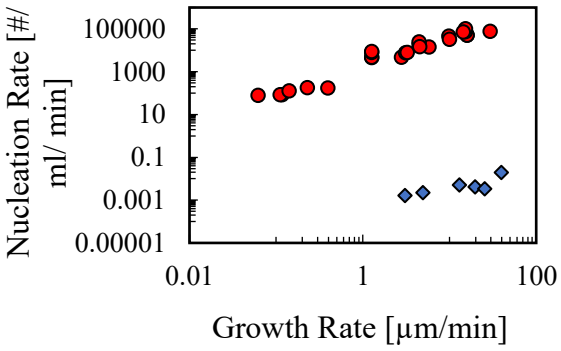

Figure 2. Primary (blue diamonds) and secondary (red circles) nucleation rates plotted vs corresponding growth rate. Secondary nucleation rate is many orders of magnitude faster than primary nucleation at all supersaturations.

CONCLUSIONS

Using a rapid small scale experimental technique utilising image analysis to quantify nucleation and growth kinetics, the metastable zone, primary and secondary nucleation kinetics and growth rates of α-glycine has been investigated. Results show that there is neither crystal growth dead zone nor secondary nucleation threshold present in this system. It is also shown that there is a close relationship between the secondary nucleation and the crystal growth rate across all supersaturations investigated. This work will provide better understanding of crystal nucleation and growth mechanisms while using rapid, small scale experiments and data analysis illustrated here should enable more facile crystallisation process development.

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